REMARKS

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 7, 9, 11, 12, 14, 17, and 18 in condition for allowance. Applicants submit that the proposed amendments of claims 7, 9, 11, 12, 14, and 17 and the addition of claim 18 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner. Applicants also submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

The Examiner has rejected claims 7, 9, 11, 12, 14, and 17 under 35 U.S.C. § 112, first paragraph for lack of enablement for reasons recited in the Office Action issued October 3, 2002. Applicants respectfully disagree with the Examiner and traverse this rejection.

The Examiner contends that "the specification does not provide for a specific asserted utility for the claimed methods in the absence of treatment of a disease" and that the only utility of the invention is for treatment of Alzheimer's Disease (AD) or amyotrophic lateral sclerosis (ALS). The pending claims, however, are not directed to the treatment of these diseases. Rather, they are directed to a method of using BMP-9 to induce the cholinergic phenotype in neurons. While this point was made by Applicants in the last response, the Examiner states that the argument is not persuasive because the only asserted utility of the invention is the treatment of neurodegenerative

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

diseases. Applicants disagree, and direct the Examiner to the additional utilities described in the specification (See page 1, lines 16-18 and page 2, lines 2-5, 13-14), specifically, the upregulation of the cholinergic phenotype and the corresponding maintenance of cognitive function.

The claims are directed generally to methods of administration of BMP-9 to induce various beneficial effects in gene expression and function in cholinergic neurons. Cholinergic neurons in the basal forebrain are important for cognition and memory. BMP-9 induces upregulation of the cholinergic phenotype. Administration of BMP-9 could, therefore, be used to induce or maintain brain function.

Having established utility of the claimed invention, Applicants now address the enablement issues. The Examiner contends that practice of Applicants' invention would require undue experimentation. Applicants submit that the specification provides all the information necessary for one skilled in the art to make and use the claimed invention, for the following reasons.

First, the Examiner contends that protein therapy in the brain is unpredictable. Applicants submit that the specification does not have to disclose what is known to one skilled in the art (*Manual of Patent Examining Procedure*, Section 2164.01), however, there are many well established techniques for delivering protein therapeutics to the brain. These include intracerebroventricular injection or infusion, intraparenchymal injection, and implantation of infusion pumps.

Applicants provide with this response, the following references describing the delivery of neurotrophic proteins to rat and human brains:

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER L.L.P.

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Klein et al. (2000) Brain Res 875:144-151;

Tuszynski (2000) Cell Transplantation 9:629-636;

Jonhagen et al. (1998) Dement Cogn Disord 9:246-257;

Wang et al. (2001) Stroke 32:2170-2178;

Hefti et al. (1994); J Neurobiol 25(11):1418-1435; and

Nabeshima et al. (2000) Alz Dis and Assoc Disord 14(Supp 1):S39-S46.

As described in these references, delivery of NGF to the brain prevented cholinergic neuron atrophy in rats (Nabeshima et al.). In humans, intracerebroventricular administration of NGF produced improvement in a number of neuropsychology tests (Jonhagen et al.). Additionally, BMP-6 has been delivered to the brain and shown to induce the desired effects (Wang et al). These results demonstrate that administration of proteins to the brain is routine practice and does not require undue experimentation. Because the brain-specific delivery of neurotrophic factors was well-known and predictable as of the filing date of this application, a demonstration of this technique in the specification is not necessary.

The Examiner also contends that "the specification does not offer a starting point that will effect the desired outcome *in vivo* in a diseased animal, nor does it provide the skilled artisan with the direction in which experimentation should proceed." Applicants point to the specification at page 7, where the formulations of the invention are disclosed; to page 8, where the modes of administration are disclosed; and page 9, where the dosages and measurements of efficacy are disclosed. In addition, the Examples clearly demonstrate that the delivery of BMP-9 to neuronal cells induces the expression of those genes known to regulate the cholinergic phenotype (Examples III-

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

VII). These teachings provide the skilled artisan with all the information necessary to practice the claimed invention. One must simply deliver a BMP-9 therapeutic to a mammal by way of one of the disclosed methods of administration, and then measure the outcome by cognitive function assessment or biochemical assays for markers of the cholinergic phenotype. These delivery methods and assays were well known to those skilled in the art before the filing date of this application. Therefore, the specification provides an excellent starting point for practicing the invention and more than enough direction for one skilled in the art to produce the predictable result of stimulating the cholinergic phenotype in a patient.

The Examiner also attempts to support the lack of enablement rejection by stating that there are no working examples and no animal models that exhibit all the essential features of AD, notably amyloid plaques and neurofibrillary tangles (10/3/02 O.A., page 4, lines 10-17). The Examiner then contends that because of the absence of animal models, any treatment of AD is unpredictable. Applicants respectfully disagree and again note that the claims are directed to the induction of the cholinergic phenotype. That an animal model does not possess all of the hallmarks of AD is not relevant to the measurement of BMP-9's effectiveness in inducing cholinergic neurons. A lack of working examples of the treatment of disease is similarly not relevant because one skilled in the art would readily understand that the teachings of BMP-9 induced upregulation of the genes associated with the cholinergic phenotype would necessarily translate into a prediction that BMP-9 would upregulate these genes in adult mouse and human tissue. No reasonable doubt has been cast on the ability of BMP-9 to perform this function.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Additionally, the Examiner states that scientists do not understand what causes AD. Scientists do, however, understand that degeneration of cholinergic neurons leads to a decreases in cognitive ability (Bartus et al.). Therefore, while the cause and effect of AD may not be completely clear, the direct result of degeneration of cholinergic neurons is quite predictable, as is the result of prevention of cholinergic neuron degeneration.

Finally, the Examiner contends that the claims are overly broad in scope, encompassing a wide range of neurodegenerative diseases. Applicants disagree. The claims are directed to the use of BMP-9 to induce the cholinergic phenotype. The fact that the claimed invention may be beneficial in the treatment of a number of symptoms of neurodegenerative diseases, namely the loss of cholinergic neurons and the corresponding loss of memory and cognitive function, does not broaden the scope of the claims beyond what is described in the specification.

In light of the above evidence and arguments, Applicants submit that the specification fully enables one skilled in the art to make and use the claimed invention without undue experimentation. Applicants respectfully request that the rejection of claims 7, 9, 11, 12, 14, and 17 under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Examiner has rejected claims 9 and 17 as indefinite under 35 U.S.C. § 112, second paragraph. The Examiner contends that the phrase "method for treating degenerating cholinergic neurons in a patient" in claim 9 is indefinite because no treatment of these neurons is achieved. Applicants have amended claim 9 to recite: "method for treating a patient with degenerating cholinergic neurons." The Examiner also contends that the phrase "method for treating malfunctioning cholinergic neurons in

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

a patient" in claim 17 is indefinite because no treatment of these neurons is achieved. Applicants have amended claim 17 to recite: "method for treating a patient with malfunctioning cholinergic neurons." Applicants submit that these amendments overcome the rejection of claims 9 and 17 under 35 U.S.C. § 112, second paragraph and request that these claims be allowed.

In view of the foregoing amendments and remarks, Applicants request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fee to deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 11, 2003

By: _____
Leslie A. McDonell
Reg. No. 34,872

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com